UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DK

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/095,536 | 06/10/98 | KINK J | GFHD-03282 |

HM12/0702

VIRGINIA S MEDLEN
MEDLEN AND CARROLL
SUITE 2200
220 MONTGOMERY STREET
SAN FRANCISCO CA 94104

| EXAMINER | |
|---|---|
| HAMUD, F | |
| **ART UNIT** | **PAPER NUMBER** |
| 1646 | 4 |

**DATE MAILED:** 07/02/99

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

file copy

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/095,536 | John A. Kink |
| **Examiner** | **Group Art Unit** |
| Fozia Hamud | 1646 |

☒ Responsive to communication(s) filed on *Aug 28, 1998*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-18* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

1. Claims 1-18 are pending and under consideration by the Examiner.

***Claim rejections-35 USC § 101***

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2a. Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-6 recite "a composition comprising a mixture of antibodies...." which encompasses the antibodies as they occur in nature. However, since Applicants do not intend to claim a naturally occurring product, amendment of the claims to show the hand of man would obviate this rejection. It is suggested that the claims be amended to recite " an isolated composition comprising .....".

***Claim rejections-35 USC § 112***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3a. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "a composition comprising a mixture of antibodies..", which renders the claim vague and indefinite because it is not clear what is meant by "a mixture", is it one to one ratio, 10% of one antibody and 90% of the other or something else? Deletion of this limitation from the claim would obviate this rejection.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4a. Claims 1-3, and 7-15 are rejected under U.S.C. § 103 as being unpatentable over Starnes et al (12-90) and Doherty et al (09/92).

Starnes et al teach that both tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) play important roles as mediators of the pathology observed in septic shock and endotoxin shock (see abstract, page 4185 and column 2 second paragraph). Starnes et al teach that inhibition of TNF-α actions by administration of specific polyclonal antibodies against TNF-α blocks the hemodynamic collapse and mortality associated with septic shock and also results in decrease in IL-6 levels after *E.coli* challenge, (page 4185, top of column 2, and page 4189, first paragraph under discussion). Using a septic shock mouse model, Starnes et al showed that monoclonal antibodies against IL-6 protected mice against lethal challenge of *E.coli* and also protected mice from mortality associated with intravenous administration of TNF-α, (page 4185, column 2 second and last paragraphs, page 4189, first paragraph under discussion and figures 4 and 5). However, Starnes et al do not disclose a composition comprising both antibodies to TNF-α and IL-6 or a method of treatment with such composition.

Doherty et al teach that both TNF-α and interferon gamma (IFN-γ) are important mediators of septic shock, (see abstract, page 1666). They also demonstrated that mice treated with either anti-

IFN-γ polyclonal antibodies or anti-TNF-α polyclonal antibodies had a dose dependent improvement in survival after a lethal dose of LPS, (see page 1669, columns 1 and 2, and figure 3, on page 1667). However, neither Starnes et al nor Doherty et al disclose a composition comprising polyclonal antibodies directed against TNF-α, IL-6 and IFN-γ and a method of treatment with such composition.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Starnes and Doherty to develop a therapeutic composition comprising anti-TNF-α, anti- IL-6 and anti-IFN-γ antibodies and a method of treatment for a mammal (human) with symptoms of sepsis or who is at risk for sepsis, by administering (intravenously, orally or parenterally) said composition, because Starnes et al teach that both TNF-α and IL-6 are important mediators of septic shock pathology and antibodies directed against each cytokine significantly altered endotoxin lethality, and Doherty et al teach that both IFN-γ and TNF-α are important mediators of septic pathophysiology, and antibodies directed against each cytokine considerably decreased the mortality of endotoxin shock. Therefore, the combined teachings of Starnes et al and Doherty et al suggest that antagonizing all three cytokines (TNF-α, IL-6 and IFN-γ) may be beneficial to human subjects or animals with severe infections and may be useful in treating or preventing sepsis.

One of ordinary skill in the art would have been motivated at the time of the invention to develop a composition comprising antibodies against TNF-α, Il-6 and IFN-γ and a method of treating sepsis with said composition, because Starnes et al and Doherty et al demonstrated that these antibodies when used separately showed beneficial effects against septic shock, thus, combining them

in one therapeutic composition would be expected to give synergistic and more robust effect against septic shock, it would also be easier to administer one composition to a patient than it is to administer three different compositions. Also sepsis is a major cause of morbidity and mortality in humans and other animals and an effective treatment is in great need. Furthermore, one of ordinary skill in the art would be motivated to use polyclonal antibodies, because polyclonal antibodies have a broader range of specificity and are easier to produce.

3b. Claims 3-6 and 16-18 are rejected under U.S.C. § 103 as being unpatentable over Starnes et al (12-90) and Doherty et al (09/92), in view of Emery et al (U.S. Patent 5,420,253).

The teachings of Starnes and Doherty et al have been set forth above. However, Starnes and Doherty et al do not disclose a composition comprising avian (chicken) anti-TNF-α, anti-Il-6 and anti-IFN-γ antibodies and a method treatment using said composition.

Emery et al teach a method for purifying high yields of IgG (IgY) immunoglobulin from chicken egg yolk (abstract). Emery et al disclose that antibodies derived from egg yolk provide significant advantage over their mammalian counterparts because they provide a higher level of specificity and reduced amount of undesirable side effects. Egg yolks contain high levels of IgG (IgY) immunoglobulin (column 1, lines 11-21), it is also less labor intensive to collect immunoglobulin-containing eggs from birds than to separate it from serum of mammals. Emery et al suggest that anti-TNF antibodies could be produced by said method (column 4, lines 43-44) and that these antibodies could be administered orally, parenterally, by suppository (rectally) or by injection when used to immunize animals and/or humans. (Column 8, lines 49-68).

Therefore, it would have been obvious to on e of ordinary skill in the art at the time of the invention to use the method taught by Emery et al to produce a composition comprising avian (chicken) polyclonal anti-TNF-α, anti-Il-6 and anti-IFN-γ antibodies, and a method of treatment for sepsis using said composition, because Emery et al teach the advantage that antibodies produced from chicken egg yolk are highly specific and patients are less likely to develop immune reactions to them that they might develop to antibodies of other non-human origin, and production of avian antibodies are more efficient and less costly.

One of ordinary skill in the art would have been motivated at the time of the invention, to produce avian polyclonal anti-TNF antibodies, anti-IL-6 antibodies and anti-IFN-γ antibodies from chicken egg yolk as taught by Emery et al, because this method would allow the production of high levels of anti-TNF-α, Anti-l-6 and anti-IFN-γ antibodies for the treatment of sepsis, in a cost-effective manner with minimum adverse side effects.

***Conclusion***

No claim is allowed.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8896. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Paula Hutzell, can be reached on (703) 308-4310.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner

ArtUnit 1646 FH
June 29, 1999

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER